Fibrinogen Receptor (GPIIb-IIIa) Antagonists Derived from 5,6-Bicyclic Templates. Amidinoindoles, Amidinoindazoles, and Amidinobenzofurans Containing the *N*-α-Sulfonamide Carboxylic Acid Function as Potent Platelet Aggregation Inhibitors

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A series of highly potent and specific fibrinogen receptor antagonists have been discovered and optimized through structural modification of the novel amidinoindole and benzofuran compounds, **I** and **II**. Systematic linker optimization afforded the amidinobenzofuran-containing inhibitor **29**, which displayed an IC_{50} value of 250 nM in platelet aggregation assays. Attempts to enhance activity by modification of the β-position of the β-alanyl carboxylate group of **29** had only a modest effect on inhibitory activity in aggregation assays. Analogues prepared to enhance the activity by conformational restriction were also found to be equally or less potent. In contrast, modification at the α-position of the β-alanyl carboxylate group resulted in the identification of extremely potent and novel amidinobenzofuran-containing derivatives **46**−**49**. Reexamination of 5,6-bicyclic aromatic nucleus led to the further identification of amidinoindole- and amidinoindazole-containing derivatives **53**−**55.** These analogues, **46**−**49** and **53**−**55,** exhibited potent in vitro activity with IC_{50} values of 25−65 nM in platelet aggregation assays and an IC_{50} value of 2 nM in fibrinogen binding assays and demonstrated a selectivity of >50000-fold for GPIIb-IIIa versus the most closely related integrin, the vitronectin receptor, $\alpha_v\beta_3$.

Introduction

Adhesion of platelets to damaged blood vessel walls or following rupture of atherosclerotic plaque initiates a series of biochemical and cellular activations that promote platelet aggregation and fibrin formation and ultimately thrombus formation, critical events in arterial thrombosis.[1,2] Fibrinogen (Fg) and other adhesive proteins bind to an activated membrane-bound glycoprotein (GP) complex, GPIIb-IIIa, found on platelets mediating the final common pathway leading to platelet aggregation.[3−5] Because of the pivotal role that platelet GPIIb-IIIa plays in thrombosis, antagonists which compete for adhesive protein binding to GPIIb-IIIa are novel antithrombotic agents for the treatment of severe arterial thrombotic conditions such as unstable angina, myocardial infarction, and stroke. With the discovery that peptides containing the arginylglycylaspartyl (RGD) sequence are capable of effectively inhibiting the binding of fibrinogen and other adhesive ligands to GPIIb-IIIa, considerable synthetic effort toward the development of RGD-based peptide and nonpeptide GPIIb-IIIa antagonists has ensued.[6−16]

Previous structure−activity studies of peptide and nonpeptide antagonists of GPIIb-IIIa have identified structural features of these inhibitors that contribute to specific GPIIb-IIIa reactivity: a basic functional group such as an amino, guanidino, or benzamidino appropriately oriented with respect to the other important functional group, which is optimally a carboxylic acid. Placing the basic and acidic functionalities at a certain distance appended to an appropriate template has been a common theme in the strategy in the design of a variety of potent nonpeptide GPIIb-IIIa antagonists. Utilizing 5-amidinoindole as an arginine isostere and appending acidic tails of varying lengths in an effort to mimic the critical distance between the guanidyl and carboxyl binding sites within the RGD sequence, McCowan et al.[17] have identified the amidinoindole acid **I** and amidinobenzofuran acid **II** as moderately potent RGD nonpeptide mimics (Figure 1). We now present further efforts undertaken to enhance the activity of this novel series of amidinoindole- and amidinobenzofuran-containing derivatives **I** and **II** and to identify leads for potential development as orally available GPIIb-IIIa antagonists. As part of this study we have examined compounds of the general structure **III** where systematic linker optimization, conformational restriction, and

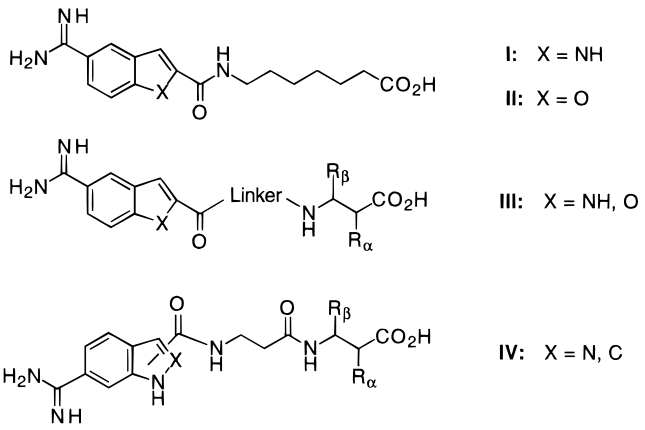

Figure 1.

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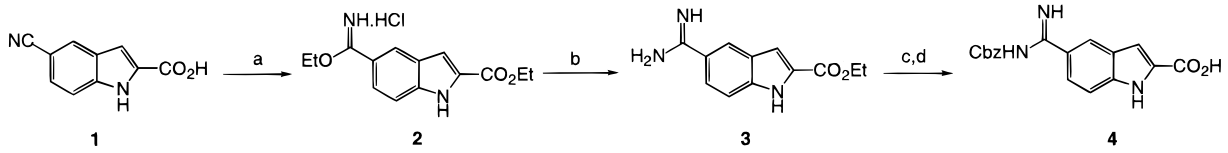
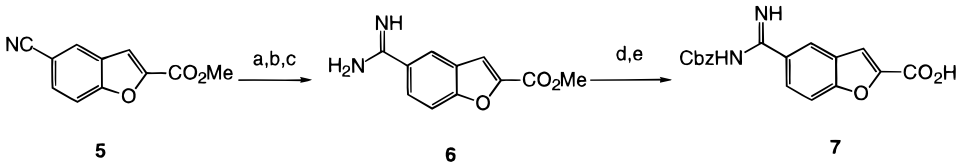
Scheme 1[a]



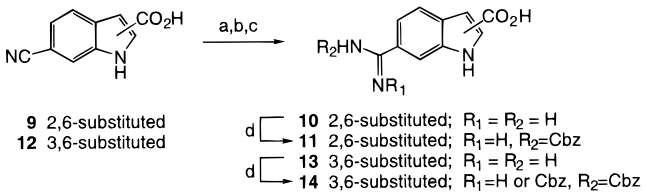
[a] (a) EtOH, HCl; (b) EtOH, NH_3; (c) Cbz-OSu, TEA, DMF; (d) LiOH, THF/H_2O.

Scheme 2[a]



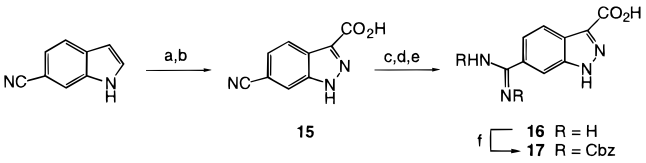
[a] (a) H_2S, Et_3N, pyridine; (b) MeI, acetone; (c) NH_4OAc, MeOH; (d) Cbz-OSu, TEA, DMF; (e) LiOH, THF/H_2O.

Scheme 3[a]



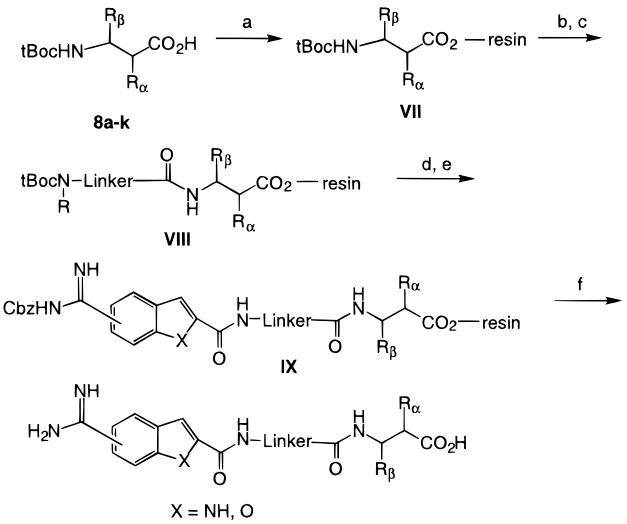
[a] (a) H_2S, Et_3N, pyridine; (b) MeI, acetone; (c) NH_4OAc, MeOH; (d) DIEA, TMS-Cl; then DIEA, Cbz-Cl.

Scheme 4[a]



[a] (a) $NaNO_2$, H_2O, HCl; (b) $NaClO_2$, NaH_2PO_4; (c) H_2S, Et_3N, pyridine; (d) MeI, acetone; (e) NH_4OAc, MeOH; (f) DIEA, TMS-Cl; then DIEA, Cbz-Cl.

Scheme 5[a]



[a] (a) Hydroxymethyl resin, BOP, DMAP, DMF; (b) (1) TFA, (2) DIEA; (c) Boc-N-linker-CO_2H, DCC, HOBt; (d) (1) TFA, (2) DIEA; (e) **4** or **7**, DCC, HOBt; (f) HF.

modification at both the α- and *β*-positions to the carboxylate group have been made. Following optimization of the general structure **III,** we reexamined the aromatic nucleus through preparation of compounds of the general structure **IV** (Figure 1). Several additional analogues with potencies comparable to those derived from general structure **III** were identified. This report describes the design, synthesis and identification of a number of GPIIb-IIIa antagonists which exhibit potent activity as platelet aggregation inhibitors as well as marked selectivity for the fibrinogen receptor, GPIIb-IIIa, versus the vitronectin receptor, $\alpha_v\beta_3$, the most closely related integrin.

Chemistry

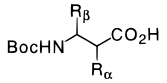
Novel amidinoindole, amidinobenzofuran, and amidinoindazole-containing inhibitors **18**−**55** were synthesized using both solution-phase and solid-phase peptide synthesis following the synthetic sequence shown in Scheme 5. The synthesis of various components utilized in these syntheses was accomplished as depicted in Schemes 1−4 and as referenced in Table 1.

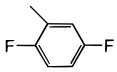
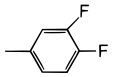
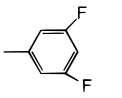
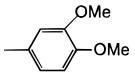
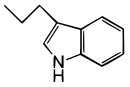
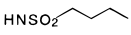
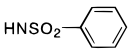
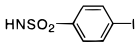
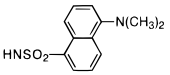
The preparation of the key protected segment, 5-Cbz-amidinoindole-2-carboxylic acid **4,** is outlined in Scheme 1. The imidate salt **2** was synthesized using Pinner conditions by passing dry hydrogen chloride into a solution of nitrile **1** in absolute ethanol at 25 °C.[17] Reaction of the crude imidate salt **2** with ammonia in absolute ethanol afforded the amidinoindole ethyl ester **3** in quantitative yield. Protection of the amidino functionality and subsequent hydrolysis of the ethyl ester gave key intermediate **4**, which is suitably protected for both solid-phase and solution chemistries.

After unsuccessful attempts to synthesize 5-amidinobenzofuran-2-carboxylic acid ester **6** employing an approach similar to that depicted in Scheme 1, an alternative known three-step protocol[18] was used for the conversion of the cyano group to the amidino group. This consisted of sequential reaction of nitrile **5**[17] with hydrogen sulfide, methyl iodide, and ammonium acetate (Scheme 2). The amidino function of the resulting 5-amidinobenzofuran-2-carboxylic acid ester **6** was protected, and the ester was hydrolyzed to give the key intermediate **7**.

The methods utilized in the preparation of the terminal carboxylic acid motifs **8a**−**k** used in the syntheses of Scheme 5 are described in the literature and are referenced as noted in Table 1. A variety of racemic *β*-aryl *β*-amino acids **8a**−**e** were prepared from the appropriate aryl aldehyde, malonic acid, and ammonium acetate via a modified Knoevenagel procedure and protected as Boc derivatives.[19] The racemic ethynyl *β*-amino acid **8f** was prepared according to a literature procedure described by Metcalf.[20] The racemic 3-[(*tert*-butoxycarbonyl)amino]-5-(3-indolyl)valeric acid **8g** was

Table 1. Methods for Preparation of Compounds **8a**−**k**



Compound	R_β	R_α	Method Reference
8a		H	19
8b		H	19
8c		H	19
8d		H	19
8e		H	19
8f		H	20
8g		H	21
8h	H		22
8i	H		22
8j	H		22
8k	H		22

synthesized following the procedure described by Duggan et al.[21] General methods as described by Egbertson and co-workers[22] were used to prepare α-substituted amino acid derivatives **8h**−**k**.

Compounds **10** and **13** (Scheme 3) were prepared from the corresponding nitriles, **9** and **12**,[17] using the same three-step process described in Scheme 2. Although all attempts to protect the amidino groups of **10** and **13** using Cbz-OSu failed, an alternate procedure utilizing in situ N-silylation of amidino acids **10** or **13** with DIEA and TMS-Cl in refluxing CH_2Cl_2 followed by addition of DIEA and then Cbz-Cl afforded **11** and **14** (50% as the bis-Cbz-protected derivative), respectively.[23]

Indazole acid **17** (Scheme 4) was prepared from 6-cyanoindole[17] by a two-stage rearrangement−oxidation procedure affording **15**. Conversion of the nitrile functionality to the bis-Cbz-protected amidino moiety as described in Scheme 3 afforded the protected indazole acid **17**.

The β- and α-substituted β-amino acids **8a**−**k** were attached through the carboxylate functionality to (hydroxymethyl)polystyrene resin using the coupling agent BOP (Scheme 5). Compounds **18**−**49** were readily assembled using standard solid-phase peptide synthesis protocols (DCC−HOBt) using an Applied Biosystems 431A peptide synthesizer. Compounds **50**−**55** were also readily synthesized using essentially the same approach as in Scheme 5 except that manual solid-phase peptide synthesis techniques were utilized in lieu of the automated system.

Results and Discussion

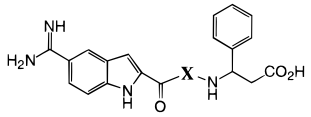
Bioassays. Three biological assays were used to assess the in vitro activity of the compounds described in this study: (i) inhibition of platelet aggregation induced by 20 μM adenosine 5′-diphosphate (ADP) in human platelet rich plasma (h-PRP), (ii) inhibition of fibrinogen binding to purified immobilized GPIIb-IIIa (integrin, $\alpha_{IIb}\beta_3$), and (iii) inhibition of vitronectin binding to the purified immobilized vitronectin receptor $\alpha_v\beta_3$ in order to determine the integrin selectivity of the compounds.[6,7] All data are given in Tables 2−7.

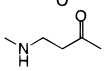
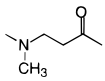
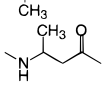
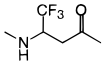
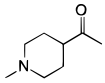
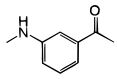
On the basis of our previous observation[17] as well as those reported in the literature for other series of integrin inhibitors, we initially targeted three regions of the lead molecule **III** for modification: the linker unit, the β-position of the carboxylate terminus, and the α-position of the carboxylate terminus. The β-phenyl-β-alanine carboxylate subunit was initially incorporated into all analogues due to the availability of the requisite starting materials and the intention to incorporate a hydrophobic group at the β-position of the carboxylate function which has been demonstrated by Scarborough et al.,[25a] Zablocki et al.,[26] and others[25b] to be beneficial for the potency in different series of GPIIb-IIIa inhibitors. We then reexamined the 5,6-bicyclic nucleus while incorporating the optimized spacer and carboxylate modifications as determined from general structure **III**.

1. Linker Modifications. Our synthetic modification of **III** focused initially on optimizing the linkage between the amidino and carboxylate functionalities using the following approaches:

(a) Introduction of *N*-α-and *C*-α-Methyl Groups as Conformational Constraints within a Variety of Amino Acid Linkers. It is known that substituting methyl groups for hydrogen atoms in the backbones of peptides decreases their available conformational space.[14] We employed this conformational restriction approach on lead compound **I** (Table 2). As a starting point for reference, the initial compound prepared contained a glycine linker (compound **18**) which displayed only modest GPIIb-IIIa inhibitory activity ($IC_{50} = 50$ μM in PRP and $IC_{50} = 10$ μM in the GPIIb-IIIa ELISA, Table 2). Replacement of the glycyl linker with the *N*-methylated glycine residue afforded **19** and led to a slight enhancement in the in vitro potency of approximately 2-fold increase in PRP assay versus **18** and no enhancement in the ELISA assay. However, the more sterically demanding C-α-dimethylated glycine analogue **20** had diminished inhibitory potency (5−10 times less active in PRP and ELISA assays) relative to **18**. Replacement of the glycyl linker with a β-alanyl linkage to afford analogue **21** enhanced the activity of **18** by approximately 6-fold in the PRP assay and 10-fold in the ELISA assay. N-α- and C-β-methylation of the β-alanine analog **21** afforded compounds **22** and **23**, which were comparable to the unsubstituted β-alanine derivative **21** in activity in platelet aggregation. Interestingly, the *N*-methyl analogue **22** was significantly more potent in the purified ligand binding assay, suggesting that the intrinsic activity against the receptor was enhanced by this modification but did not translate into a corresponding enhancement of activity in the aggregation assay. This may be due to increased plasma protein binding of this analogue in the PRP assay as has been noted in other GPIIb-IIIa inhibitors.[17] A *C*-β-trifluoromethyl-containing compound **24** dis-

Table 2. Linker Modification of Lead Compound **I**



Compound	X	IC$_{50}$ (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
18		50	10	ND[3]
19		25	10	ND[3]
20		250	>100	ND[3]
21		8	1	ND[3]
22		5	0.02	>100
23		5	2.5	125
24		50	10	ND[3]
25		25	6	ND[3]
26		25	50	ND[3]
27		5	ND[3]	ND[3]

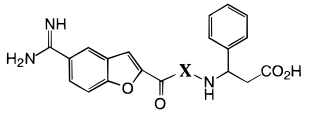
1. Concentration required to reduce ADP (20 μM) induced human platelet aggregation response by 50% for the PRP assay. A minimum of two determinations were made for each compound. 2. Concentration required to reduce binding of fibrinogen to purified GPIIb-IIIa by 50% or the concentration required to reduce binding of vitronectin to purified $\alpha_v\beta_3$ by 50%. A minimum of two determinations were made for each compound. The average error for the assay was ±15%. 3. Not Determined.

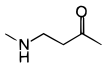
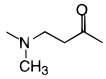
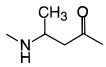
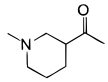
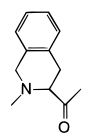
played lower potency than the β-methyl-containing compound **23**, which may be due to electronic rather than steric factors.

In the corresponding amidinobenzofuran-containing series, the reference glycyl-containing inhibitor **28** was enhanced to the same degree by replacement with the β-alanine linker, compound **29**, which was 30-fold more potent than amidinoindole-containing compound **21** in the aggregation assay and 6-fold more potent in the ligand binding assay (Table 3). Attempts to introduce conformational restrictions through N-α-and C-β-methylation of the β-alanine linker (**30**, **31**) again did not enhance the activity over **29** in the aggregation assay. In this series of analogues, the β-methyl-β-alanyl-containing compound displayed a 5−7-fold enhancement in the ELISA assay compared to **29**, but a similar enhancement in the PRP assay was not observed. However, since the goal of this effort was to prepare analogues which displayed superior activity in plasma, where these agents must exert their activity in vivo, the relative activities of analogues in PRP is important and guided our efforts.

(b) Replacement of Glycine and β-Alanine by More Rigid Linkers. To determine whether the additional or alternate conformational restriction within the linker would modulate activity, glycine or β-alanine

Table 3. Linker Modification of Lead Compound **II**



Compound	X	IC$_{50}$ (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
28		2	0.3	ND[3]
29		0.25	0.15	60
30		0.25	0.15	>100
31		0.5	0.02	>100
32		0.25	0.4	ND[3]
33		2	1	ND[3]
34		50	50	ND[3]
35		5	0.5	ND[3]

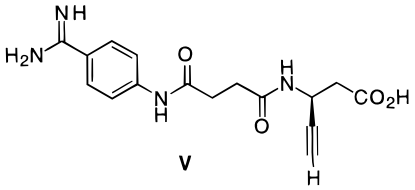
1. As in Table 2.
2. As in Table 2.
3. Not Determined.

residues were replaced by several rigid cyclic linkers. These modifications which included the incorporation of the 3-piperidine carboxyl, prolyl, and tetrahydroisoquinoline-3-carboxyl linkers resulted in equally potent analogues (**33** and **35** related to **28**, **32** related to **29**; see Table 3) in the amidinobenzofuran series. While only a limited number of substitutions were studied, they were generally tolerated. However, conformational restriction introduced by these substitutions did not necessarily enhance the activity within this series. The 25-fold difference in activity observed for **33** versus **34** suggests a receptor preference for the *S*-configuration at the α-position of the rigid linker proline.

For both series of compounds, insertion of a simple β-alanyl linker produced compounds **21** and **29** with enhanced activity of approximately 10-fold in PRP assays and 2-fold in the ELISA assay relative to the corresponding glycine-containing analogues **18** and **28**. This result reemphasizes the importance of the distance between the amidino and carboxylic acid.

On the basis of the in vitro potency and synthetic accessibility, the amidinobenzofuran **29**, which contained the unsubstituted β-alanyl linker, was chosen as a lead for further structural optimization directed at the α- and β-positions of the carboxylic acid terminus.

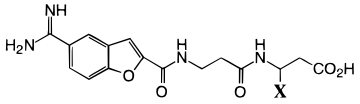
2. Modification at the β-Position of the Carboxylate Terminus. Numerous studies of GPIIb-IIIa inhibitors have suggested that residues at or very near the aspartic acid of the RGD sequence modulate the selectivity of ligand binding to integrins, and introduction of aromatic or other hydrophobic residues proximal to the RGD site can significantly enhance the inhibitory



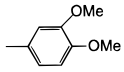
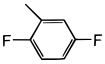
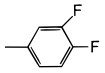
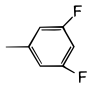
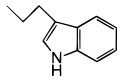
V

Figure 2.

Table 4. Effects of β-Substitution on Platelet Aggregation and Adhesive Protein Binding to Purified Integrins



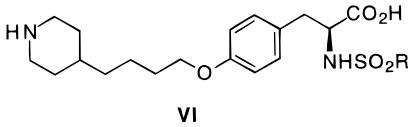
X

Compound	X	IC$_{50}$ (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
29		0.25	0.15	60
36	H	0.28	0.02	>100
37	CF_3	0.25	0.04	>100
38		0.3	0.04	>100
39		0.2	0.04	100
40		0.3	0.04	ND[3]
41		0.3	0.125	>100
42		0.5	0.2	>100
43		0.35	0.1	>100
44		0.6	ND[3]	ND[3]

1. See previous Tables
2. See previous Tables
3. Not Determined.

activity and specificity of the RGD analogues.[25] On the basis of an extensive SAR study at a position β to the carboxylic acid terminus in a different series of GPIIb-IIIa inhibitors, Zablocki et al.[26] have recently reported the potent platelet aggregation inhibitor **V** (Figure 2). In our series, we have utilized a similar approach to study the effect of β-substitutions to the carboxylic acid on the interaction of amidinobenzofuran-containing analogues with GPIIb-IIIa.

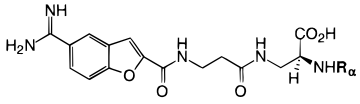
A series of analogues related to 3-phenyl-β-alanine derivative **29** were prepared (analogues **36**−**44**; Table 4). When the β-phenyl group was replaced by other nonaromatic residues such as H, CF_3, or alkynyl, these analogues (**36**−**38**) were not significantly different in potency from the phenyl containing analogue **29** in the aggregation assay, but had moderate (~4-fold) increase in activity in the ELISA assay. While it was anticipated that increasing the electron-withdrawing or -donating ability of the ring system would modulate the inhibitory activity of the analogues, varying the phenyl ring substituent had only modest effects on analogue activity as shown in Table 4 in both the PRP and ELISA assays. These β-substituted amidinobenzofuran-containing acid

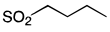
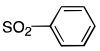
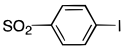
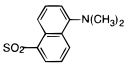


VI

Figure 3.

Table 5. Effects of α-Substitution on Platelet Aggregation and Adhesive Protein Binding to Purified Integrins



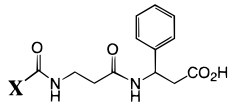
Compound	R_α	IC$_{50}$ (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
45	H	0.2	0.04	>100
46		0.035	0.002	>100
47		0.035	0.0018	>100
48		0.025	0.002	>100
49		0.065	0.002	>100

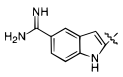
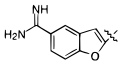
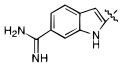
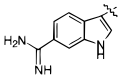
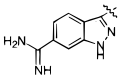
1. See previous Tables.
2. See previous Tables.

analogues displayed IC_{50} values of 0.2−0.6 μM for inhibition of ADP-mediated platelet aggregation. Less than a 3-fold difference in platelet aggregation inhibition and fibrinogen binding inhibition in the ELISA assay was observed between the most and least potent inhibitors in this series of phenyl-substituted analogues. The overall similar potency of compounds **37**−**44** suggests that the moiety at the position β to the carboxylic acid terminus interacts with a region of GPIIb-IIIa that is capable of accepting a fairly broad range of hydrophobicities, electronegativities, and molecular volumes. The compounds in this series also did not have any appreciable activity with the vitronectin receptor, $\alpha_v\beta_3$. These observations, coupled with our goal to increase the activity at least 10-fold relative to analogue **29**, prompted us to further investigate the effects of α-substitution in the interaction of these analogues with GPIIb-IIIa.

3. Modification at the α-Position of the Carboxylate Terminus. Egbertson et al.[22] and Hartman et al.[11] have reported that in a different series of tyrosine-containing GPIIb-IIIa inhibitors introduction of sulfonyl substituents on the α-amino group of compound **VI** (Figure 3) resulted in a class of very potent and specific inhibitors of GPIIb-IIIa. This modification has also been applied to other series[27] but is not uniformly successful in enhancing the GPIIb-IIIa inhibitory activity of compounds.[28] In our series, the free α-amino-containing analogue **45** was nearly equipotent to the unsubstituted analogue **36**. Incorporation of the butanesulfonamido functionality into the carboxylic acid terminus afforded analogue **46** which displayed a 6-fold enhancement in activity in the platelet aggregation assay and approximately 20-fold enhancement in the ligand binding assay (IC_{50} = 2.0 nM) relative to **45** (Table 5). Similarly, several α-arylsulfonamide-substituted amidinobenzofuran-containing acids (**47**−**49**) were prepared which were found to be nearly equivalent to butanesulfonamide **46**.

Table 6. Effects of Aromatic Amidine Nucleus Modification



Compound	X	IC_{50} (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
21		8	1	ND[3]
29		0.25	0.15	60
50		1.35	ND[3]	ND[3]
51		2.2	ND[3]	ND[3]
52		0.63	ND[3]	ND[3]

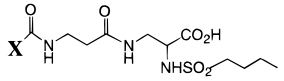
1. See previous Tables.
2. See previous Tables.
3. Not Determined.

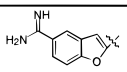
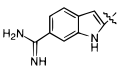
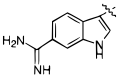
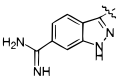
4. Modification of the 5,6-Bicyclic Nucleus. Having identified compound **29** as an early lead, we were interested in briefly reexamining the 5,6-bicyclic nucleus to determine whether additional modifications in this region of the molecules could further enhance potency. As such, compounds **50**−**52** were prepared and evaluated relative to compounds **21** and **29** (see Table 6). While these modifications resulted in 3−13-fold improved potency in the platelet aggregation assay relative to indole-containing **21** (IC_{50} = 8 μM), they did not display enhanced activity over benzofuran-containing **29** (IC_{50} = 0.25 μM). The relative potencies of **50**, **51**, and **52** versus **29** were, however, generally consistent with the pattern previously observed[17] for the same aromatic nuclei in a different series of inhibitors. Namely, the 2,6-substituted indole-containing compound **50** and the 3,6-substituted indole-containing compound **51** were approximately 5−9-fold weaker inhibitors of platelet aggregation than benzofuran-containing compound **29** while the 3,6-substituted indazole-containing compound **52** was more potent than either **50** or **51**. Although in the previously reported series of inhibitors[17] the indazole-containing compound was found to be more potent than the corresponding benzofuran-containing compound, in this series indazole-containing **52** was 2.5-fold weaker than benzofuran-containing **29**.

Even though these modifications resulted in a 2.5−10-fold loss in potency relative to compound **29**, the same aromatic nuclei were substituted into the α-sulfonamido series in order to study the potency-enhancing effect of this functionality in conjunction with slightly less than optimal aromatic nuclei (Table 7). Indeed, compounds **53**−**55** demonstrated a 10−40-fold increase in potency in the PRP assay over compounds **50**−**52**. They were also found to be equivalent to compounds **46**−**49** in both the PRP and binding assays, as well as in integrin selectivity.

While the modifications to the 5,6-bicyclic nucleus did not result in compounds which were more potent analogues than **29** or **46**, the data did suggest that the potential presence or absence of an H-bond acceptor in the 5-membered ring of the 5,6-bicyclic nucleus modulates the potency in this series. For example, benzofuran-containing compound **29** is 30-fold more potent in the PRP assay and 6-fold more potent in the ELISA assay than the corresponding indole-containing compound **21**. The main difference between these two compounds is the presence of the oxygen in **29** which is a better H-bond acceptor than is the N−H in compound **21**. Likewise, indazole-containing compound **52** is 3-fold better in the platelet aggregation assay than is the corresponding indole-containing compound **51** with the main difference being the presence of the second nitrogen in **52**, which also may be acting as an H-bond acceptor. An alternate explanation for these observed differences may be that the basicity of the amidino group has been affected, thereby altering the potency of the compounds. Our data cannot distinguish between these or other possible explanations for the activities in this series.

Table 7. Effects of Aromatic Amidine Nucleus Modifications in the Sulfonamide Series



Compound	X	IC_{50} (μM) PRP[1]	Fg/GPIIb-IIIa[2]	Vn/$\alpha_v\beta_3$[2]
46		0.035	0.002	>100
53		0.055	ND[3]	ND[3]
54		0.050	0.002	>100
55		0.053	0.002	>100

1. See previous Tables.
2. See previous Tables.
3. Not Determined.

As shown in Tables 5 and 7, analogues **46**−**49** and **53**−**55** were by far the most potent analogues prepared in this study. This result suggests that a hydrophobic sulfonamide at the α-position enhances the binding of this class of compounds to GPIIb-IIIa. These observations are consistent with the results published by Hartman et al.[11] and Egbertson et al.[22] who have proposed that the α-sulfonamide substituents may be interacting with an unexploited "exosite" contained within the GPIIb-IIIa complex. The observation that modifications of the phenyl ring in the β-position of **29** resulting in compounds **39**−**44** did not have significant effects on potency might be due to the fact that these various β-substituents could be interacting with this exosite. A similar lack of variability in potencies is present for analogues **46**−**49** and **53**−**55**, all of which contain an α-sulfonamide functionality. A comparison of the PRP data for compounds **29**, **51**, and **52** (about a 10-fold range) relative to **46**, **54**, and **55** (less than 2-fold in PRP and ELISA assays) demonstrates that the incorporation of an α-sulfonamide into an inhibitor in this series can override other potency modulating characteristics of the molecule such as the presence of an H-bond acceptor in the 5,6-bicyclic nucleus. The fact that several different aromatic rings in the sulfonamide

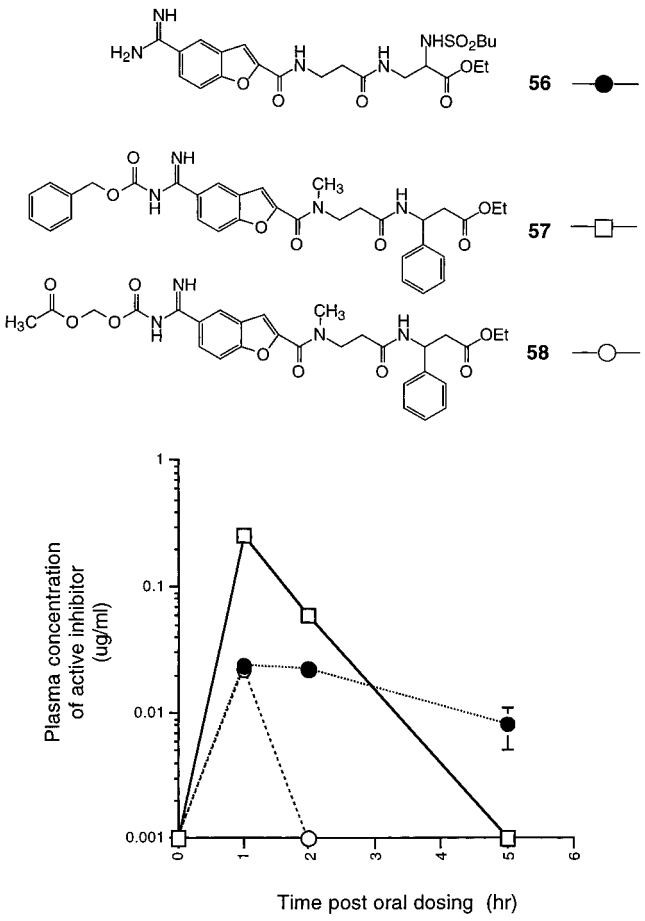


Figure 4. Plasma concentration of active species after oral administration of **56**, **57**, or **58**.

moieties in compounds **47**−**49** were well tolerated suggests that modifications in this portion of the molecules may allow for modulation of oral absorption profiles, while retaining potent GPIIb-IIIa activity.

Prodrugs of the more potent analogues (**30** and **46**) were prepared using standard peptide-coupling procedures. The ethyl ester of analogue **46** was obtained as its single ethyl ester prodrug, analogue **56**.[29] Additionally the *N*-[(acyloxy)methoxy]carbonyl group[30a,b] or the carbobenzyloxy group was added to the amidine function of the ethyl ester of analogue **30** to afford the double prodrugs **57** and **58**, respectively.[29] The single prodrug **56** and the double prodrugs **57** and **58** were evaluated in vivo in rats following oral administration at a dose of 10 mg/kg. Determination of the plasma levels achieved over time of the parent carboxylic acids **30** and **46** were consistently low and suggest poor oral bioavailability of these inhibitors (Figure 4). While many of the analogues in this series display potent in vitro activity, their potential as leads in the identification of orally available inhibitors was not realized.

Conclusions

In summary, we have reported the discovery and optimization of a class of amidinoindole-, amidinoindazole-, and amidinobenzofuran-containing acid compounds which function as potent GPIIb-IIIa antagonists and which are also effective inhibitors of platelet aggregation. Structural optimization of the lead compounds **I**, **II**, and **III** at the linker unit, at the β- and α-positions of the carboxylate function, and at the aromatic nucleus has provided very potent and specific antagonists **46**−**49** and **53**−**55** ($IC_{50} = 0.025-0.065\ \mu M$ in aggregation assays). The integrin specificity in this series may, in part, be attributed to the presence of an aryl amidino which serves as the base which replaces the arginine guanidine in RGD sequences as has been previously observed.[8,11] The 10-fold to 40-fold potency enhancement of analogues **46**−**49** and **53**−**55** compared to their corresponding β-substituted analogues **37**−**44** and **50**−**52** is likely due to their interaction with a previously postulated "exosite" on GPIIb-IIIa by the sulfonamide functionality.

Experimental Section

^{1}H NMR spectra were recorded on a Varian Unity + 400 spectrometer unless otherwise noted. Low-resolution mass spectra were recorded with a Vestec 201XL analytical spectrometer performed at SRI International, with an ABI Bio-Ion 20 mass spectrometer performed at Chiron Mimotopes Peptide Systems or with a Perkin-Elmer SCIEX API-I performed at Synpep Corp. High-resolution mass spectra were recorded with a VG ZAB2-EQ high-resolution mass spectrometer and performed at the University of California at Berkeley. Normal-phase silica gel (EM Science, silica gel 60) was used for chromatography. Final compounds were purified by reverse phase HPLC using a Waters 4000Prep, Waters 490E multiwavelength detector, and Vydac 218TP1022 column (10 μm, C_{18}, 22 × 250 mm). Purity of the compounds were confirmed by two diverse HPLC systems using Waters 600 controller, Waters 996 photodiode array detector and Vydac 201HS54 column (5 μm, C_{18}, 4.6 × 250 mm).

5-(Cbz-Amidino)indole-2-carboxylic Acid (4). (a) Ethyl 5-Amidinoindole-2-carboxylate (3). A slurry of 5-cyanoindole-2-carboxylic acid (**1**) (7 g, 37.6 mmol) in 800 mL of EtOH was treated with a stream of HCl gas for 2 h. The resulting solution was capped, stirred at room temperature for 64 h, and evaporated in vacuo to afford **2**. The residue was reconstituted in EtOH, and the mixture was treated with a stream of NH_3 gas for 1 h. The reaction mixture was stirred at room temperature overnight and was concentrated to afford **3** as a solid (10.72 g): ^{1}H NMR (CD_3OD) δ 9.12 (b, 1H), 8.56 (b, 1H), 8.22 (s, 1H), 7.64 (m, 2H), 7.32 (s, 1H), 4.4 (q, $J = 7$ Hz, 2H), 1.4 (t, $J = 7$ Hz, 3H); exact mass (FAB, M + 1)$^+$ calcd 232.1086, found 232.1089.

(b) Ethyl 5-(Cbz-amidino)indole-2-carboxylate. A mixture of ethyl 5-amidinoindole-2-carboxylate (**3**) (3.27 g, 12.2 mmol), *N*-(benzyloxycarbonyloxy)succinimide (3.04 g, 12.2 mmol), and triethylamine (3.4 mL, 24.4 mmol) in DMF (150 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, and the organic layer was washed with water three times, dried (anhydrous Na_2SO_4), filtered, and evaporated to yield the title compound as a white solid (4.52 g, 100%): ^{1}H NMR (CD_3OD) δ 8.25 (m, 1H), 7.64 (m, 2H), 7.49−7.34 (m, 6H), 5.39 (s, 2H), 4.4 (q, $J = 7$ Hz, 2H), 1.4 (t, $J = 7$ Hz, 3H); exact mass (FAB, M + 1)$^+$ calcd 366.1454, found 366.1445.

(c) 5-(Cbz-Amidino)indole-2-carboxylic Acid (4). A solution of ethyl 5-(Cbz-amidino)indole-2-carboxylate (4.4 g, 12 mmol) in THF (25 mL) was treated with LiOH (1.5 g, 36 mmol) and H_2O (25 mL). The mixture was stirred at room temperature overnight. The organic solvent was evaporated in vacuo. The aqueous layer was extracted with EtOAc and acidified to pH 3−4 with 2 N aqueous HCl at 0 °C. The resulting solid was filtered and dried to give the corresponding acid **4** as a white solid (3.77 g, 93.3%): ^{1}H NMR (CD_3OD) δ 8.24 (m, 1H), 7.64 (m, 2H), 7.47 (m, 2H), 7.39 (m, 3H), 7.33 (bs, 1H), 5.38 (s, 2H); exact mass (FAB, M + 1)$^+$ calcd 338.1141, found 338.1139.

5-(Cbz-Amidino)benzofuran-2-carboxylic Acid (7). (a) Methyl 5-Amidinobenzofuran-2-carboxylate (6). A solution of methyl 5-cyanobenzofuran-2-carboxylate (**5**) (4.48 g, 22.3 mmol) in pyridine/TEA, 5:1 (200 mL), was saturated with H_2S and stirred at room temperature until no starting material could be detected by TLC. Excess H_2S was extruded by a gentle stream of nitrogen, and the solvents were removed to give the corresponding thioamide (5.3 g, 99%) as a yellow solid.

A solution of the thioamide (5.3 g, 22.3 mmol) and iodomethane (14 mL, 223 mmol) in acetone (250 mL) was heated to reflux until no starting material could be detected by TLC. Complete removal of the solvents yielded the corresponding thioiminomethyl ester as a yellow salt. This material and ammonium acetate (6.86 g, 89 mmol) in methanol (180 mL) was heated to reflux for 1 h. The mixture was evaporated in vacuo, and the resulting oil was triturated with THF to give a solid which was collected by filtration, washed (THF), and dried to give the title compound **6** (5.24 g, 100%): ^{1}H NMR (CD_3OD) δ 8.25 (s, 1H), 7.86 (m, 2H), 7.75 (s, 1H), 3.96 (s, 3H); exact mass (FAB, M + 1)$^+$ calcd 219.0770, found 219.0766.

(b) 5-(Cbz-Amidino)benzofuran-2-carboxylic Acid (7). Compound **7** was synthesized by the same method for **4** using **6** in place of **3**: ^{1}H NMR (CD_3OD) δ 8.24 (m, 1H), 7.83 (m, 2H), 7.64 (s, 1H), 7.48 (m, 2H), 7.393 (m, 3H), 5.39 (s, 2H); MS (FAB) 339.0 (M + 1)$^+$.

6-Amidinoindole-2-carboxylic Acid (10). Compound **10** was synthesized by the same method for **6** using **9** in place of **5**: ^{1}H NMR (CD_3OD) δ 7.96 (t, J = 0.7 Hz, 1H), 7.82 (d, J = 8.46 Hz, 1H), 7.43 (dd, J = 8.46, 1.84 Hz, 1H), 7.11 (d, J = 1.1 Hz, 1H); MS (DCI-NH_3) 204 (M + 1)$^+$.

6-(Cbz-amidino)indole-2-carboxylic Acid (11). To a suspension of 6-amidinoindole-2-carboxylic acid (**10**) (1.15 g, 5.7 mmol) in anhydrous DCM (14 mL) at room temperature under argon was added DIEA (6.0 mL, 34 mmol) followed by slow addition of TMS-Cl (4.4 mL, 34 mmol). The resulting solution was warmed to 40 °C, stirred for 1.5 h, and then cooled to 0 °C. Another addition of DIEA (6.0 mL, 34 mmol) was followed by Cbz-Cl (4.9 mL, 34 mmol). After the mixture was stirred at 0 °C for 15 min and then at room temperature for 3 h, the reaction was quenched by the careful addition of 3 N HCl (25 mL). The resulting suspension was cooled to 0 °C and stirred vigorously for 15 min and filtered and the solid rinsed with H_2O and air-dried for 1 h. This solid was then suspended in 50 mL of THF and mixed thoroughly, and DCM (50 mL) was added. After being cooled to −78 °C, the solid was filtered, rinsed with DCM (50 mL), and dried under high vacuum to afford pure title compound **11** (1.271 g, 66%) as an off-white powder: ^{1}H NMR (CD_3OD) δ 7.99 (t, J = 1.1 Hz, 1H), 7.91 (dd, J = 8.45, 1.1 Hz, 1H), 7.45 (m, 6H), 7.27 (d, J = 1.47 Hz, 1H), 5.43 (s, 2H); MS (LC-MS) 338 (M + 1)$^+$.

6-Amidinoindole-3-carboxylic Acid (13). Compound **13** was synthesized by the same method for **6** using **12** in place of **5**: MS (DCI-NH_3) 204 (M + 1)$^+$.

6-(Cbz-amidino)indole-3-carboxylic Acid (14). Compound **14** (as a mixture with 50% di-Cbz protected as determined by RP-HPLC) was synthesized by the same method for **11** using **13** in place of **10**: MS (DCI-NH_3) 338 and 472 (M + H)$^+$.

6-Cyano-1*H*-indazole-3-carboxylic Acid (15). To 6-cyanoindole (1.42 g, 10.0 mmol) suspended in a solution of $NaNO_2$ (6.9 g, 100 mmol) in H_2O (200 mL) at room temperature was slowly added 6 N HCl (15 mL) until the pH was <2. After the resulting suspension was stirred for 3 h, it was extracted with EtOAc (5 × 150 mL). The EtOAc was dried over $MgSO_4$, filtered, and removed in vacuo to afford 3-formyl-6-cyanoindazole (100%) which was subsequently oxidized without further purification: ^{1}H NMR (d_6-DMSO) δ 10.2 (s, 1H), 8.35 (s, 1H), 8.25 (d, J = 8.06 Hz, 1H), 7.65 (d, J = 8.06 Hz, 1H); MS (EI) 171 (M$^+$).

To a mixture of 3-formyl-6-cyanoindazole (10.0 mmol) and 2-methyl-2-butene (40 mL) in DMF (70 mL) at 0 °C was added over 20 min a freshly prepared solution of $NaClO_2$ (9 g, 0.10 mol) and $NaH_2PO_4 \cdot H_2O$ (11 g, 80 mmol) in H_2O (80 mL). This reaction mixture was then stirred at room temperature until complete by TLC and RP-HPLC. The reaction was acidified by slow addition of 6 N HCl (40 mL) followed by stirring for 2 h. Water (250 mL) was added, and the solution was washed with EtOAc (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and solvent removed under reduced pressure to give 3 g of the crude acid. Trituration with 100 mL of DCM followed by filtration and rinsing with an additional 50 mL of DCM afforded 1.212 g (65% from 6-cyanoindole) of the title compound **15** as an off-white solid: ^{1}H NMR (d_6-DMSO) δ 8.28 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 6.1 Hz, 1H); MS (EI) 187 (M$^+$).

6-Amidino-1*H*-indazole-3-carboxylic Acid (16). Compound **16** was synthesized by the same method for **6** using **15** in place of **5**: MS (DCI-NH_3) 205 (M + 1)$^+$.

6-(Bis-Cbz-amidino)-1*H*-indazole-3-carboxylic Acid (17). Compound **17** was synthesized by the same method for **11** using **16** in place of **10**: ^{1}H NMR (CD_3OD) δ 8.70 (d, J = 1.0 Hz, 1H), 8.46 (d, J = 8.79 Hz, 1H), 7.78 (dd, J = 8.42, 1.47 Hz, 1H), 7.57 (d, J = 6.59 Hz, 2H), 7.50 (d, J = 6.23 Hz, 2H), 7.40 (m, 6H), 5.60 (s, 2H), 5.42 (s, 2H); MS (DCI-NH_3) 473 (M + 1)$^+$.

General Procedure for the Attachment of Substituted *β*-Amino Acids to Hydroxymethyl Resin. Example 1. D,L-3-(Boc-amino)-3-phenylpropionic Acid Hydroxymethyl Resin. Hydroxymethyl resin (4 g, 0.749 mequiv of OH/g) was suspended in DMF (40 mL). D,L-3-(Boc-amino)-3-phenylpropionic acid (Aldrich) (3.18 g, 12 mmol), DMAP (0.37 g, 3 mmol), DIEA (2.79 mL, 15 mmol), and BOP were added. The mixture was rocked at room temperature overnight. The resulting resin was collected in a fritted glass Buchner funnel, washed with MeOH and DCM, and dried in vacuo.

3-[[2-(5-Amidino-2-indolecarboxamido)acetyl]amino]-3-phenylpropionic Acid (18). Compound **18** was synthesized by standard automated solid-phase synthesis protocols using an Applied Biosystems 431A peptide synthesizer (Foster City, CA). D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin from example 1 described above was deprotected with 50% TFA/DCM followed by coupling with *N*-Boc-glycine. The Boc group was removed again with 50% TFA/DCM followed by coupling with 5-(Cbz-amidino)indole-2-carboxylic acid **4**. Completed compound was released from the hydroxymethyl resin along with deprotection of the side chains using standard hydrogen fluoride cleavage methods. It was purified to homogeneity using reversed-phase high-performance liquid chromatography: ^{1}H NMR (CD_3OD) δ 8.19 (s, 1H), 7.62 (s, 2H), 7.32 (m, 6H), 5.37 (m, 1H), 4.08 (s, 2H), 2.82 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 408.1672, found 408.1661.

3-[[2-(*N*-Methyl-5-amidino-2-indolecarboxamido)acetyl]amino]-3-phenylpropionic Acid (19). Compound **19** was synthesized by the same method for **18** using *N*-Boc-*N*-methylglycine in place of *N*-Boc-glycine: exact mass (FAB, M + 1)$^+$ calcd 422.1828, found 422.1825.

3-[[2-(*N*,*N*′-Dimethyl-5-amidino-2-indolecarboxamido)acetyl]amino]-3-phenylpropionic Acid (20). Compound **20** was synthesized by the same method for **18** using *N*-Boc-2,2′-dimethylglycine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H), 7.62 (s, 2H), 7.32 (m, 6H), 5.36 (m, 1H), 2.82 (m, 2H), 1.62 (s, 3H), 1.58 (s, 3H); exact mass (FAB, M + 1)$^+$ calcd 436.1985, found 436.1985.

3-[[3-(5-Amidino-2-indolecarboxamido)propionyl]amino]-3-phenylpropionic Acid (21). Compound **21** was synthesized by the same method for **18** using *N*-Boc-*β*-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.19 (s, 1H), 7.62 (s, 2H), 7.20 (m, 6H), 5.37 (t, 1H), 3.60 (t, 2H), 2.78 (m, 2H), 2.58 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 422.1828, found 422.1825.

3-[[3-(*N*-Methyl-5-amidino-2-indolecarboxamido)propionyl]amino]-3-phenylpropionic Acid (22). Compound **22** was synthesized by the same method for **18** using *N*-Boc-*N*-methyl-*β*-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.19 (s, 1H), 7.62 (s, 2H), 7.21 (m, 6H), 5.37 (t, 1H), 3.83 (m, 2H), 3.29 (m, 3H), 2.78 (m, 2H), 2.62 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 436.1985, found 436.1977.

3-[[3-(5-Amidino-2-indolecarboxamido)-3-methylpropionyl]amino]-3-phenylpropionic Acid (23). Compound **23** was synthesized by the same method for **18** using *N*-Boc-α-methyl-*β*-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.19 (s, 1H), 7.62 (s, 2H), 7.23 (m, 6H), 5.35 (t, 1H), 4.47 (m, 1H), 2.76 (m, 2H), 2.50 (m, 2H), 1.27 (d, 3H); exact mass (FAB, M + 1)$^+$ calcd 436.1985, found 436.1987.

3-[[3-(5-Amidino-2-indolecarboxamido)-3-(trifluoromethyl)propionyl]amino]-3-phenylpropionic Acid (24). Compound **24** was synthesized by the same method for **18** using *N*-Boc-α-(trifluoromethyl)-*β*-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 7.64 (s, 2H), 7.30 (m, 6H), 5.27 (m, 2H), 2.80 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 490.1702, found 490.1699.

3-[[*N*-[(5-Amidino-2-indolyl)carbonyl]isonipecotyl]-amino]-3-phenylpropionic Acid (25). Compound **25** was synthesized by the same method for **18** using *N*-Boc-isonipecotic acid in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.18 (s, 1H), 7.61 (s, 2H), 7.30 (m, 6H), 5.33 (t, 1H), 4.50 (bs, 2H), 3.40 (m, 1H), 3.00 (m, 1H), 2.79 (m, 2H), 2.60 (m, 1H), 1.80 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 462.2142, found 462.2144.

3-[[3-(5-Amidino-2-indolecarboxamido)benzoyl]amino]-3-phenylpropionic Acid (26). Compound **26** was synthesized by the same method for **18** using 3-Boc-aminobenzoic acid in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.10−7.20 (m, 13H), 5.50 (m, 1H), 2.90 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 470.1828, found 470.1829.

3-[[*N*-[(5-Amidino-2-indolyl)carbonyl]-L-prolyl]amino]-3-phenylpropionic Acid (27). Compound **27** was synthesized by the same method for **18** using *N*-Boc-L-proline in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.10−7.20 (m, 9H), 5.35 (m, 1H), 4.23 (m, 1H), 3.29 (m, 2H), 2.80 (m, 2H), 1.93 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 448.1985, found 448.1976.

3-[[2-(5-Amidino-2-benzofurancarboxamido)acetyl]-amino]-3-phenylpropionic Acid (28). Compound **28** was synthesized by the same method for **18** using 5-(Cbz-amidino)-benzofuran-2-carboxylic acid **7** in place of 5-(Cbz-amidino)-indole-2-carboxylic acid **4**: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.84 (m, 2H), 7.62 (s, 1H), 7.35 (m, 5H), 5.38 (t, 1H), 4.09 (s, 2H), 2.83 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 409.1512, found 409.1510.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-phenylpropionic Acid (29). Compound **29** was synthesized by the same method for **28** using *N*-Boc-β-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 7.80 (dd, 2H), 7.59 (s, 1H), 7.30 (m, 2H), 7.18 (m, 3H), 5.39 (t, 1H), 3.62 (m, 2H), 2.80 (m, 2H), 2.59 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 423.1668, found 423.1673.

3-[[3-(*N*-Methyl-5-amidino-2-benzofurancarboxamido)-propionyl]amino]-3-phenylpropionic Acid (30). Compound **30** was synthesized by the same method for **28** using *N*-Boc-*N*-methyl-β-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.21 (m, 1H), 7.85 (m, 2H), 7.44 (s, 1H), 7.31 (m, 5H), 5.34 (m, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.20 (s, 3H), 2.80 (m, 2H), 2.60 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 437.1825, found 437.1822.

3-[[3-(5-Amidino-2-benzofurancarboxamido)-3-methyl-propionyl]amino]-3-phenylpropionic Acid (31). Compound **31** was synthesized by the same method for **28** using *N*-Boc-α-methyl-β-alanine in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.20 (s, 1H), 7.80 (m, 2H), 7.59 (d, 1H), 7.30 (m, 3H), 7.10 (m, 2H), 5.39 (t, 1H), 4.48 (t, 1H), 2.80 (m, 2H), 2.50 (m, 2H), 1.30 (d, 3H); exact mass (FAB, M + 1)$^+$ calcd 437.1825, found 437.1835.

3-[[*N*-[(5-Amidino-2-benzofuranyl)carbonyl]nipecotyl]-amino]-3-phenylpropionic Acid (32). Compound **32** was synthesized by the same method for **28** using *N*-Boc-nipecotic acid in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.60 (s, 1H), 8.20 (s, 1H), 7.70 (m, 2H), 7.20 (m, 5H), 5.33 (t, 1H), 4.20 (m, 3H), 3.10 (m, 1H), 2.80 (m, 2H), 2.58 (m, 1H), 1.80 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 463.1981, found 463.1977.

3-[[*N*-[(5-Amidino-2-benzofuranyl)carbonyl]-L-prolyl]-amino]-3-phenylpropionic Acid (33). Compound **33** was synthesized by the same method for **28** using *N*-Boc-L-proline in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.22 (m, 1H), 7.83 (s, 1H), 7.00−7.60 (m, 7H), 5.34 (m, 1H), 5.00 (m, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 2.80 (m, 2H), 2.20 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 449.1825, found 449.1820.

3-[[*N*-[(5-Amidino-2-benzofuranyl)carbonyl]-D-prolyl]-amino]-3-phenylpropionic Acid (34). Compound **34** was synthesized by the same method for **28** using *N*-Boc-D-proline in place of *N*-Boc-glycine: ^{1}H NMR (CD_3OD) δ 8.20 (m, 1H), 7.80 (m, 1H), 7.00−7.60 (m, 7H), 5.34 (m, 1H), 5.00 (m, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 2.80 (m, 2H), 2.20 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 449.1825, found 449.1825.

3-[[*N*-[(5-Amidino-2-benzofuranyl)carbonyl]tetrahydroisoquinolyl]amino]-3-phenylpropionic Acid (35). Compound **35** was synthesized by the same method for **28** using *N*-Boc-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid in place of *N*-Boc-glycine: MS (DCI) 511 (M + 1)$^+$.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]propionic Acid (36). Compound **36** was synthesized by the same method for **29** using *N*-Boc-β-alanine hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.82 (m, 2H), 7.60 (s, 1H), 3.65 (t, 2H), 3.42 (t, 2H), 2.50 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 347.1355, found 347.1362.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(trifluoromethyl)propionic Acid (37). Compound **37** was synthesized by the same method for **29** using D,L-*N*-Boc-amino-α-(trifluoromethyl)-β-alanine hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 7.82 (m, 2H), 7.60 (s, 1H), 5.0 (t, 1H), 3.65 (t, 2H), 2.56 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 415.1229, found 415.1227.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-ethynylpropionic Acid (38). Compound **38** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-4-pentynoic acid **8f** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.84 (t, 2H), 7.60 (s, 1H), 5.00 (m, 2H), 3.66 (m, 2H), 3.50 (m, 2H), 2.67 (s, 1H), 2.42 (t, 1H); exact mass (FAB, M + 1)$^+$ calcd 371.1355, found 371.1353.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(3′-pyridyl)propionic Acid (39). Compound **39** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-3-(3′-pyridyl)propionic acid **8e** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.75 (s, 1H), 8.55 (d, 1H), 8.29 (m, 1H), 8.23 (s, 1H), 7.80 (m, 3H), 7.57 (s, 1H), 5.40 (t, 1H), 3.65 (t, 2H), 2.93 (m, 2H), 2.58 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 424.1621, found 424.1628.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(3′,4′-dimethoxyphenyl)propionic Acid (40). Compound **40** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-3-(3′,4′-dimethoxyphenyl)propionic acid **8d** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.86 (dd, 2H), 7.55 (s, 1H), 6.90 (m, 2H), 6.76 (d, 1H), 5.32 (t, 1H), 3.67 (m, 2H), 2.78 (m, 2H), 2.58 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 483.1880, found 483.1882.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(2′,5′-difluorophenyl)propionic Acid (41). Compound **41** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-3-(2′,5′-difluorophenyl)propionic acid **8a** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 7.84 (dd, 2H), 7.58 (s, 1H), 7.00 (m, 3H), 5.53 (t, 1H), 3.63 (t, 2H), 2.78 (m, 2H), 2.58 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 459.1480, found 459.1486.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(3′,4′-difluorophenyl)propionic Acid (42). Compound **42** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-3-(3′,4′-difluorophenyl)propionic acid **8b** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 7.82 (dd, 2H), 7.56 (s, 1H), 7.21 (m, 1H), 7.10 (m, 2H), 5.31 (t, 1H), 3.65 (m, 2H), 2.75 (m, 2H), 2.56 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 459.1480, found 459.1477.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(3′,5′-difluorophenyl)propionic Acid (43). Compound **43** was synthesized by the same method for **29** using D,L-3-(Boc-amino)-3-(3′,5′-difluorophenyl)propionic acid **8c** hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 7.84 (dd, 2H), 7.58 (s, 1H), 6.92 (t, 2H), 6.71 (m, 1H), 5.32 (t, 1H), 3.65 (t, 2H), 2.77 (m, 2H), 2.58 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 459.1480, found 459.1483.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-3-(2-indol-3-ylethyl)propionic Acid (44). Compound **44** was synthesized by the same method for **29** using D,L-3-(*N*-Boc)-3-(2-(indol-3-yl)ethyl)-β-alanine **8g**[21] hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.06 (d, 1H), 7.75 (t, 1H), 7.61 (t, 1H), 7.52 (s, 1H), 7.37 (t, 1H), 7.23 (t, 1H), 6.98 (t, 1H), 6.93 (s, 1H), 6.86 (t, 1H), 4.31 (m, 1H), 3.68 (m,

2H), 2.60 (m, 6H), 1.85 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 490.2090, found 490.2080.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-2-aminopropionic Acid (45). Compound **45** was synthesized by the same method for **29** using L-α-Z-β-Boc-diaminopropionic acid hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.85 (m, 2H), 7.80 (s, 1H), 3.70 (m, 5H), 2.51 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 362.1464, found 362.1459.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-2-[(butylsulfonyl)amino]propionic Acid (46). Compound **46** was synthesized by the same method for **29** using 2(*S*)-[(*n*-butylsulfonyl)amino]-3-[*N*-(*tert*-butyloxycarbonyl)amino]propionic acid[22] hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: MS (ES) 482 (M + 1)$^+$.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-2-[(phenylsulfonyl)amino]propionic Acid (47). Compound **47** was synthesized by the same method for **29** using 2(*S*)-[(phenylsulfonyl)amino]-3-[*N*-(*tert*-butyloxycarbonyl)amino]propionic acid hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.24 (s, 1H), 7.82 (m, 4H), 7.59 (m, 4H), 4.11 (t, 1H), 3.65 (m, 4H), 2.52 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 502.1396, found 502.1383.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-2-[[(*p*-iodophenyl)sulfonyl]amino]propionic Acid (48). Compound **48** was synthesized by the same method for **29** using 2(*S*)-[[(*p*-iodophenyl)sulfonyl]amino]-3-[*N*-(*tert*-butyloxycarbonyl)amino]propionic acid hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.23 (s, 1H), 7.85 (m, 4H), 7.64 (s, 1H), 7.55 (m, 2H), 3.92 (t, 1H), 3.65 (m, 4H), 2.53 (m, 2H); exact mass (FAB, M + 1)$^+$ calcd 628.0363, found 628.0357.

3-[[3-(5-Amidino-2-benzofurancarboxamido)propionyl]-amino]-2-[(dansylsulfonyl)amino]propionic Acid (49). Compound **49** was synthesized by the same method for **29** using 2(*S*)-[(dansylsulfonyl)amino]-3-[*N*-(*tert*-butyloxycarbonyl)amino]propionic acid hydroxymethyl resin in place of D,L-3-(Boc-amino)-3-phenylpropionic acid hydroxymethyl resin: ^{1}H NMR (CD_3OD) δ 8.51 (d, 1H), 8.40 (d, 1H), 8.21 (m, 2H), 7.84 (m, 2H), 7.62 (m, 3H), 7.33 (d, 1H), 4.07 (t, 1H), 3.57 (m, 2H), 2.91 (s, 6H), 2.25 (m, 4H); exact mass (FAB, M + 1)$^+$ calcd 595.1975, found 595.1988.

3-[[3-(6-Amidino-2-indolecarboxamido)propionyl]amino]-3-phenylpropionic Acid (50). Compound **50** was synthesized by the same method for **18** using compound **11** in place of **4**, and manual solid-phase peptide synthesis (as described in example 1) was utilized in place of the automated system: MS (ES) 422 (M + 1)$^+$.

3-[[3-(6-Amidino-3-indolecarboxamido)propionyl]amino]-3-phenylpropionic Acid (51). Compound **51** was synthesized by the same method for **50** using compound **14** in place of **11**: ^{1}H NMR(CD_3OD) δ 8.30 (d, 1H), 8.03 (s, 1H), 7.95 (d, 1H), 7.54 (dd, 1H), 7.30 (dd, 2H), 7.19 (m, 3H), 5.36 (t, 1H), 3.64 (dq, 2H), 2.79 (dq, 2H), 2.56 (dd, 2H); exact mass (FAB, M + 1)$^+$ calcd 422.1828, found 422.1837.

3-[[3-(6-Amidino-1*H*-3-indazolecarboxamido)propionyl]-amino]-3-phenylpropionic Acid (52). Compound **52** was synthesized by the same method for **50** using compound **17** in place of **11**: ^{1}H NMR(CD_3OD) δ 8.45 (d, 1H), 8.10 (s, 1H), 7.58 (dd, 2H), 7.30 (dd, 2H), 7.26 (m, 3H), 5.35 (t, 1H), 3.69 (t, 2H), 2.77 (dq, 2H), 2.57 (t, 2H); exact mass (FAB, M + 1)$^+$ calcd 422.1781, found 422.1779.

3-[[3-(6-Amidino-2-indolecarboxamido)propionyl]amino]-2-[(butylsulfonyl)amino]propionic Acid (53). Compound **53** was synthesized by the same method for **46** using compound **11** in place of **7**, and manual solid-phase peptide synthesis (as described in example 1) was utilized in place of the automated system: MS (ES) 481 (M + H)$^+$.

3-[[3-(6-Amidino-3-indolecarboxamido)propionyl]amino]-2-[(butylsulfonyl)amino]propionic Acid (54). Compound **54** was synthesized by the same method for **53** using compound **14** in place of **11**: ^{1}H NMR (CD_3OD) δ 8.32 (d, 1H), 8.15 (s, 1H), 7.94 (dd, 1H), 7.55 (dd, 1H), 4.21 (dd, 1H), 3.68 (m, 2H), 3.32 (t, 2H), 3.02 (t, 2H), 2.54 (t, 2H), 1.74 (m, 2H), 1.40 (q, 2H), 0.91 (t, 3H); exact mass (FAB, M + 1)$^+$: calcd 481.1869, found 481.1873.

3-[[3-(6-Amidino-1*H*-3-indazolecarboxamido)propionyl]-amino]-2-[(butylsulfonyl)amino]propionic Acid (55). Compound **55** was synthesized by the same method for **53** using compound **17** in place of **11**: ^{1}H NMR (CD_3OD) δ 8.36 (d, 1H), 8.02 (s, 1H), 7.51 (d, 2H), 4.15 (dd, 1H), 3.65 (m, 2H), 3.27 (s, 2H), 2.95 (t, 2H), 2.51 (t, 2H), 1.67 (m, 2H), 1.35 (dd, 2H), 0.84 (t, 3H); exact mass (FAB, M + 1)$^+$: calcd 482.1822, found 482.1817.

Platelet Aggregation Assays. Platelet aggregation was measured at 37 °C in a Chrono-log whole blood aggregometer (Chrono-log Corp.; Havertown, PA) performed in human platelet-rich plasma (PRP) prepared from blood of human donors who had not taken aspirin within the previous 10 days. Fifty-one milliliters of whole blood was drawn into 9 mL of sodium citrate (3.8%) and centrifuged at 160*g* for 20 min and allowed to stand for 5 min, and PRP was decanted into a clean tube. Platelet poor plasma (PPP) was prepared from the PRP by further centrifugation at 2000*g* for 10 min, removed with a pipet, and used in the reference cell of the aggregometer. Test substances dissolved in water or 5% aqueous DMSO were added to PRP to a final volume of 0.5 mL and allowed to incubate for 1 min followed by the addition of ADP (20 μM final) to initiate aggregation. Platelet aggregation was quantitated by measuring the total amplitude on a chart recorder. IC_{50} values were determined from dose−response curves generated from various concentrations of the purified compounds added to PRP.

Solid-Phase Ligand Binding Assays. The effect of compounds on the binding of adhesive proteins to GPIIb-IIIa and $\alpha_v\beta_3$ were determined using the solid-phase microtiter assays as described.[31,32] Purified integrins were added to microtiter wells of enzyme-linked immunosorbant assay plates (Immunlon II, Dynatech, Inc.) at 1 μg/well in 100 μL of buffer A (20 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mM $CaCl_2$, 0.02% azide) and incubated overnight at 4 °C. At the time of the experiment, the wells were washed with buffer B (50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM $CaCl_2$, 0.02% azide) and 100 μL/well of buffer B plus 35 mg/mL BSA added for 2−3 h at room temperature to block nonspecific binding. After this incubation, the plate was washed with buffer B plus 1 mg/mL BSA. Biotinylated adhesive proteins were added to wells at a final concentration of 20 nM along with various concentrations of test compounds and the plate incubated at room temperature for 3 h. The plate was again washed in buffer B plus 1 mg/mL BSA and bound biotinylated protein quantified by the addition of Sigma mouse anti-biotin antibody (100 μL/well of 1:2500 dilution) conjugated to alkaline phosphatase. Following a 1 h room temperature incubation, the wells were washed with buffer B plus 1 mg/mL BSA, and 100 μL of the substrate *p*-nitrophenyl phosphate was added (Bio-Rad kit). The color development was read after 10 min on a Molecular Devices plate reader at 405 nm.

Oral Dosing of Prodrugs to Rats. Sprague−Dawley rats were fasted overnight and dosed by oral gavage. The compounds (**56**−**58**) were formulated in 50% poly(ethylene glycol) 300 at 3 mg/mL and administered at 10 mg/kg. Blood was collected under Isoflurane anesthesia into 3.8% trisodium citrate (9:1) and plasma was prepared for subsequent analysis by HPLC.

Plasma Analysis Procedure. Plasma (0.2 mL) was mixed with 0.8 mL of pH 2 phosphate buffer containing internal standard and then extracted using IST Isolute C2 (EC) extraction cartridges. The extracts were analyzed by HPLC using an acetonitrile/pH 3 sodium dodecyl sulfate mobile phase and an Inertsil 150 × 3.2 mm column maintained at 40 °C with UV detection at 235 nm. The standard curves for analogues **30** and **46** were linear from 10 to 5120 ng/mL.

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